IDS never got it

On April 19, 2001, we filed with the USPTO an Information Disclosure Statement including the 1449 form and copies of references for the above identified application. Having received no acknowledgement of this filing from the Examiner, we resubmitted a duplicate form 1449 on October 30, 2002. We have not received an initialed copy of the 1449 form. Please forward to me a copy of the initialed 1449 form at your earliest convenience.

OK

Rejection under 35 USC §102

The Examiner has rejected Claims 1-6 under 35 USC §102(a) as allegedly anticipated by McCormick, et al. (Rationale, Design, and Baseline Characteristics, Amer. J. of Cardiology, 1997, Vol. 80, pp 1130-1133) which discusses whether aggressive treatment with atorvastatin is an alternative to angioplasty.

Applicants submit that McCormick, et al., is a disclosure by the present inventor which was made less than one year prior to the filing of the priority document, United States Provisional Patent Application Serial No. 60/102,457, filed September 30, 1998; and therefore, is not a reference for the present application. The present application is a 371 of PCT/US99/15385 filed July 8, 1999, which claims benefit of US 60/102,457, filed September 30, 1998. The publication date of McCormick, et al. is November 1, 1997. Thus, the publication is less that one year prior to the filing of the patent application. Attached to the present response is a Declaration under 37 C.F.R. § 1.132 in which the Applicant, Donald Black, re-avers that he is the inventor of the subject matter described and claimed in the present application and that the other co-authors were not involved in the conception or reduction to practice of the invention. Operating under the direction of Donald Black, Lisa McCormick was the study coordinator for the study described in the paper. David Waters, M.D., W. Virgil Brown, M.D., and Bertram Pitt, M.D. were members of the steering committee that directed the study described in the paper. The invention disclosed in the subject application was made before the formation of that steering committee. Steering committee members were involved in study logistics and the logistics of steering committee operations and were not involved in the conception of the study itself.

Applicant declares that these named co-authors of McCormick, et al. were not involved with the conception or reduction to practice of the subject invention. Thus, in accord with the Court of Customs and Patent Appeals holding in In re; Katz, 215 USPQ 14 (C.C.P.A.), Applicant submits that

McCormick, et al. is a publication of Applicant's own work published within one year of the effective filing date of

the subject application, and is therefore, not prior art under 35 USC §102(a). Therefore, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 1-6.

The Examiner has rejected Claims 1-3 under 35 USC §102(e) as being anticipated by Seed, et al. US Pat. No. 5,861,399 citing "line 62 of col. 2 through line 20 of col. 3."

A claim is anticipated only if each and every element as set forth in the claim is found in the prior art reference (see, Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). The present claims are directed toward a method for preventing or delaying catheter-based revascularization in patients suffering from coronary artery disease and in need of such treatment comprising administering a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol. The present application discloses that by administering to a patient a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol such patients are less likely to encounter an adverse cardiac event within the following 18 months as compared with patients who had undergone angioplasty (13% versus 21%, page 25, lines 5-24). Furthermore, the present application discloses that by administering to a patient a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol, such patients who were originally candidates for angioplasty were able to remain on drug therapy alone with a statistically lower likelihood of experiencing any adverse cardiovascular events over the following 18 months. Nothing in the prior art had concluded that drug therapy alone could prevent or delay the need for coronary catheter-based surgical intervention.

Seed, et al. discloses a method for **reducing a coronary artery stenosis** by at least 20%, that involves the administration of a cholesterol-lowering therapeutic, **combined with dietary restrictions**. Seed discloses ten patient case studies in which the patients were treated with dietary restrictions along with a variety of drugs, including statins, niacin, buspirone and aspirin. In contrast, the present invention provides a method for preventing or delaying catheter-based revascularization comprising administering a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol without a requirement for dietary restriction.

The treatments disclosed in Seed do not describe or teach administering a cholesterol-lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol, and thus, Seed does not disclose a required element of the claimed invention. Seed discloses that the cholesterol synthesis inhibitor is administered at greater than or equal to 10mg/day. Seed exemplifies, in case reports,

specific doses of 20, 40 mg/day of lovastatin and 10, 20, 40 mg/day of simvastatin and 10, 20 and 20-40 mg/day of pravastatin. (Col 5, line 54 – Col 14, line 20) These doses of statins are not equivalent to doses that the instant specification teaches. The instant specification teaches that for atorvastatin an amount effective to cause an aggressive lowering of LDL is about 50 to 150 mg/day (p 5, lines 19-22). Shown below are data from the PDR reference, Cardiovascular Prescribing Guide, 4th Edition (2000) (copies of relevant sections are enclosed for the Examiner's convenience), which indicate the LDL lowering effects of various statins. These data show that even the highest doses specifically disclosed by Seed do not yield the aggressive lowering of LDL as taught by the specification of the present invention. A dose of 50 mg/day atorvastatin is not specifically shown in the reference. However, values are given for doses of 40 and 80 which indicate that a 50 mg/day dose would lower LDL-C by at least 50% whereas even the highest doses of statins exemplified in Seed would yield at most a 41% reduction in LDL-C.

Values indicate LDL-C mean % change from baseline

mg/day	atorvastatin	simvastatin	lovastatin	pravastatin
10	-34	-30		-22
20	-43	-38	-24	-32
40	-50	-41	-30	-34
80*	-60			

*For lovastatin the dose is 40 mg b.i.d.

Thus, the amounts of cholesterol-lowering agent disclosed in Seed would not themselves lead to an aggressive lowering of LDL. Seed discloses treating with a cholesterol-lowering agent in combination with specific dietary requirements to achieve a lowering of LDL. Whereas the disclosure of the present application is the first demonstration that treatment with a cholesterol lowering agent on its own could prevent or delay the need for catheter-based revascularization.

Furthermore, Seed does not disclose a method for preventing or delaying catheter-based revascularization, and thus, Seed does not disclose a required element of the claimed invention. Disclosure of a reduction in stenosis of 20% is not the same as disclosure of a method that prevents or delays catheter-based revascularization. A reduction in stenosis of 20% does not mean that the need for catheter-based revascularization in that patient would be prevented or delayed. The current understanding of the manner in which coronary plaque leads to the occurrence of a cardiac event is that the plaque ruptures and leads to the coronary event. Thus, it is not the size of the stenosis, but rather the

instability of the stenosis that is correlated with cardiac events. Therefore, Seed does not reasonably convey to one of skill in the art that a method of reducing stenosis by 20% would prevent or delay catheter-based revascularization. Thus, Seed does not disclose the element that the method is for preventing or delaying catheter-based revascularization.

Because McCormick is not valid prior art to Claims 1-6 of the present invention and Seed fails to set forth each and every element of pending claims 1-3, withdrawal of the rejections under 35 USC §102(a) and §102(e) is respectfully requested.

Rejection under 35 USC §103(a)

The Examiner has rejected Claims 1-4 and 9-10 under 35 USC §103(a) as being unpatentable over Whitney, et al. US Pat No. 6,180,660 in view of Jeevanandam, et al. US Pat No. 5,957,916. The Examiner notes that "Whitney et al lacks the express written disclosure that the revascularization procedure is catheter based. The Examiner then states that "Jeevanandam, et al. teaches that it is well known in the art to perform revascularization procedures with catheters." "Therefore, it would have been obvious . . . to modify the method disclosed by Whitney, et al. to perform the method in order to prevent or delay catheter-based revascularization. This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness under 35 USC §103(a), three basic criteria must be met: 1) The prior art reference must teach or suggest all the claim limitations; 2) There must be some suggestion or motivation to modify the reference or to combine reference teachings; and 3) There must be a reasonable expectation of success. Also, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP 2142

Whitney discloses a method for preventing or reducing the risk of a first occurrence of a cardiovascular event (i.e. 'primary prevention') using an HMG-CoA reductase inhibitor alone or in combination with another lipid altering agent. The term "cardiovascular event" is defined in Whitney as including among other things, coronary revascularization procedures. Whitney also discloses useful HMG-CoA reductase inhibitors such as atorvastatin. However, Whitney further discloses that subjects to be treated are those having an average serum total cholesterol, an average to mildly elevated serum LDL-cholesterol level, and a below average serum HDL-cholesterol level, with no history of clinically evident coronary disease. As stated above, the presently claimed methods are directed toward preventing or delaying catheter-based revascularization in patients suffering from coronary artery disease (i.e. 'secondary prevention' – an intrinsically more advanced state of underlying disease) while

Whitney requires that the subject have no history of clinically evident coronary heart disease prior to the initial administration.

Applicant asserts that Jeevanandam is not analogous art to the present invention. Therefore, is not available to cite as prior art against the present invention. Jeevanandam does not teach or suggest the use of a non-surgical method for treatment of coronary artery disease. Jeevanandam is silent as to revascularization with drug therapy. Jeevanandam discloses a device and method for making channels in the inside of the heart ventricle to perfuse the myocardium. Jeevanandam discloses using a laser method of revascularization which creating transmural channels from the epicardial surface for use in treating patients in whom bypass surgery is not possible. Jeevanandam does not simply teach a surgical alternative to the method of the present invention. The surgical procedure of Jeevanandam is very different from the more common catheter-based revascularization procedures (such as angioplasty) that the present invention prevents or delays. Jeevanandam is method of using a laser to essentially poke holes in the heart muscle. In contrast, the more common procedures such as angioplasty involve a re-opening of blocked coronary arteries. For the reasons above, Applicant asserts that Jeevanandam is not analogous art to the present invention. The present invention involves a non-surgical, drug based, method of delaying or preventing catheter-based revascularization. In addition, Jeevanandam teaches only a surgical method of revascularization. One of skill in the art looking for a non-surgical method to prevent or delay a catheter-based revascularization would not look to Jeevanandam for its teachings.

The prior art does not teach or suggest all the claim limitations of the present invention.

The Examiner's rejection implies that the method of Whitney is the same as that of the instant invention except that it is not taught to prevent the need for catheter-based revascularization. This is simply not the case. Whitney does not teach or suggest all elements of Applicant's claimed invention. The present invention requires **patients suffering from coronary artery** disease be administered a cholesterol lowering agent in amount effective to cause an aggressive lowering of LDL. Whitney does not teach or suggest a method, as in the presently claimed invention, of treating patients suffering from coronary artery disease. Whitney fails to disclose anything about the non-surgical treatment of patients suffering from coronary artery disease. As discussed above, Whitney requires that the subject have no history of clinically evident coronary heart disease prior to the initial administration of the lipid altering agent.

The present invention requires patients suffering from coronary artery disease be administered a cholesterol lowering agent **in amount effective to cause an aggressive lowering of LDL**. There is no teaching or suggestion in Whitney of the requirement that the cholesterol lowering agent be administered in an amount effective to cause an aggressive lowering of LDL cholesterol. While Whitney discloses that HMG-CoA reductase inhibitors may be given at doses of about 1 to about 200 mg/day and more preferably from about 5 to 160 mg/day. Whitney more specifically exemplifies doses of 5, 10, 20, 40 and 80 mg/day for simvastatin , lovastatin and fluvastatin sodium and 10, 20, and 40 mg/day for pravastatin sodium. It is well known that potencies of the various statins differ in their ability to lower LDL. This is relevant in this discussion because the highest dose of simvastatin, lovastatin or fluvastatin specifically disclosed in Whitney is 80 mg/day which corresponds to about **40, 20, and 10** mg/day, respectively, of atorvastatin. Similarly, 40 mg/day of pravastatin corresponds to about **10** mg/day of atorvastatin. (Roberts, W.C. Excerpta Medica, Inc., 106-7, 1997) A copy of this reference has been included for the convenience of the Examiner. The PDR reference, Cardiovascular Prescribing Guide, 4th Edition (2000) has similar data supporting the relative potencies of the statins as given above. The data in the table below are excerpted from the PDR (copies of relevant portions are included for the convenience of the Examiner) and shows the % change in LDL levels for various doses of atorvastatin and the statins that are disclosed in Whitney.

value indicate LDL-C mean % change from baseline

mg/day	atorvastatin	simvastatin	lovastatin	fluvastatin	pravastatin
10	-34	-30			-22
20	-43	-38	-24	-22	-32
40	-50	-41	-30	-25	-34
80*	-60	-47	-40	-35.9	

*For lovastatin the dose is 40 mg b.i.d.

In contrast to the doses described in Whitney, the present invention requires a dose that aggressively lowers LDL. The instant specification teaches that for atorvastatin a dose that aggressively lowers LDL is about 50 to 150mg/day for an adult of normal weight (p5, lines 19-22). This dose range is significantly higher than the doses specifically suggested by Whitney which correspond with 10-40 mg/day of atorvastatin.

Finally, while Whitney does mention in passing that the methods contained therein "may be used to prevent . . .a first occurrence of a fatal or non-fatal cardiovascular event." Where "the term cardiovascular event includes, but is not limited to fatal and non-fatal acute major coronary events, **coronary revascularization procedures**, peripheral vascular disease, stable angina . . ." Whitney does not teach or suggest that treatment with a cholesterol lowering drug could prevent or delay catheter-based revascularization in patients **suffering from coronary artery disease.** Whitney focuses on prevention of a first occurrence of a cardiovascular event. The patients of the present invention have more advanced coronary disease well past the point of a first occurrence as defined in Whitney and are "suffering from coronary artery disease".

Even assuming that Jeevanandam is available as analogous prior art, Jeevanandam cannot make up for the deficiencies of Whitney. While Jeevanandam does describe two methods of catheter-based revascularization, Jeevanandam is silent as to revascularization with drug therapy. Thus, Jeevanandam cannot overcome the deficiencies of Whitney as discussed above.

There is no suggestion or motivation to modify the reference or to combine reference teachings.

Neither Whitney nor Jeevanandam include a suggestion or motivation to modify the Whitney reference to arrive at the present invention. In other words, one of ordinary skill in the art would not have been motivated to modify a method of treating subjects with no history of coronary artery disease to yield a method to prevent or delay catheter-based revascularization in a patient suffering from coronary artery disease as required in the present invention. As discussed above, Whitney discloses a method of reducing risk of a **first** occurrence of a cardiovascular event. Nothing in Whitney suggests treating patients already suffering from coronary artery disease by administering a cholesterol-lowering agent. Additionally, there is no suggestion in Whitney that the cholesterol-lowering agent be administered in an amount effective to cause an aggressive lowering of LDL cholesterol. Jeevanandam does not contain any motivation to modify the method of Whitney to arrive at the present invention. Jeevanandam discloses two methods of revascularization for patients unable to undergo bypass surgery and does not teach or suggest anything in relation to how or if one could avoid the need for revascularization. One of skill in the art would not have been motivated by the disclosure of Jeevanandam to turn to a non-surgical method to prevent or delay the surgical method taught in Jeevanandam.

There would not have been a reasonable expectation of success

Even assuming there was motivation to combine Whitney and Jeevanandam, neither the references individually or combined, provide a reasonable expectation of success that administering a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol could actually prevent or delay catheter-based revascularization in patients suffering from coronary artery disease. Neither Jeevanandam nor Whitney disclose anything about the non-surgical treatment of patients suffering from coronary artery disease. It is in Applicant's disclosure that the support for prevention or delay of catheter-based revascularization in patients suffering from coronary artery disease is found. Applicant is the first to show that high doses of a cholesterol lowering drug reduce the incidence of an adverse cardiac event from 21% to 13%. Thereby, decreasing the need for revascularization. (p 25, lines 5-24). To establish a *prima facie* case of obviousness, the reasonable expectation of success must be found in the prior art references not in the Applicant's disclosure.

Because Whitney and Jeevanandam fail to teach or suggest all of the claimed elements, fail to provide motivation to combine the references and fail to provide a reasonable expectation of success, withdrawal of the rejection of claims 1-4 and 9-10, under 35 USC §103(a), is respectfully requested.

The Examiner has rejected claims 1-6 under 35 USC §103(a) as being unpatentable over Bocan et al. WO 97/16184 in view of Jeevanandam. The Examiner states, "Bocan, et al. lacks the express disclosure of performing the method to prevent or delay catheter based revascularization." This rejection is respectfully traversed.

Bocan teaches the lowering of LDL by a combination of an acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitor and an HMG-CoA inhibitor. Bocan discloses that the resulting plasma lipoprotein profile is associated with a decreased "risk" of coronary artery disease. Bocan disclose generally that doses of HMG-CoA reductase inhibitors comtemplated for use are about 5 to 80 mg per day (page 5, lines 1-4). Bocan relies on animal data to show lowering of LDL by the combination of an ACAT inhibitor and an HMG-CoA inhibitor.

As discussed above, Jeevanandam discloses two methods of revascularization for patients unable to undergo bypass surgery, and does not teach or suggest anything in relation to how or if one could avoid the need for revascularization.

The prior art does not teach or suggest all the claim limitations of the present invention.

The Examiner's rejection implies that the method of Bocan is the same as that of the instant invention except that it is not taught to prevent the need for catheter-based revascularization. This is simply not the case. The present invention requires patients suffering from coronary artery disease be administered a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL. Bocan does not teach or suggest all elements of Applicant's claimed invention. Bocan does not teach or suggest administration of an amount of a cholesterol-lowering agent effective to cause an aggressive lowering of LDL cholesterol. While Bocan does disclose that doses contemplated are from about 5 to 80 mg/day, this disclosure teaches a broad range and does not teach or suggest to one of skill in the art to select the higher doses in that range. Nor is there a teaching or suggestion of a method for preventing or delaying catheter-based revascularization. Bocan relies on animal data and discloses that following combination treatment with an ACAT inhibitor and an HMG-CoaA inhibitor the lipoprotein profile obtained is associated with a decreased risk of coronary artery disease. "Risk" is an epidemiological term implying a greater likelihood of coronary disease. "Risk" is not tantamount to the actual demonstration of reduction in coronary ischemic events associated with aggressive cholesterol-lowering in a human population having existing coronary artery disease. Thus, Bocan does not teach or suggest that the method disclosed in Bocan can be used to prevent or delay catheter-based revascularization in human patients. Even assuming that Jeevanandam is available as analogous prior art, Jeevanandam cannot make up for the deficiencies of Bocan. While Jeevanandam does describe two methods of catheter-based revascularization, Jeevanandam is silent as to revascularization with drug therapy. Thus, Jeevanandam cannot overcome the deficiencies of Bocan as discussed above.

There is no suggestion or motivation to modify the reference or to combine reference teachings

Neither Bocan nor Jeevanandam include a suggestion or motivation to modify the Bocan reference to arrive at the present invention. Bocan does not teach or suggest that by regulating lipid concentrations one would prevent or delay catheter-based revascularization as is claimed in the present application. Bocan does not provide motivation to administer an amount of a cholesterol-lowering agent to cause an aggressive lowering of LDL cholesterol. Jeevanandam does not contain any motivation to modify the method of Bocan to arrive at the present invention. Jeevanandam discloses two methods of revascularization for patients unable to undergo bypass surgery and does not teach or suggest anything in relation to how or if one could avoid the need for revascularization. One of skill in the art would not

have been motivated by the disclosure of Jeevanandam to turn to a non-surgical method to prevent or delay the surgical method taught in Jeevanandam.

There would not have been a reasonable expectation of success.

Even assuming there was motivation to combine Bocan and Jeevanandam and assuming the present invention was suggested, neither the references individually or combined, provide a reasonable expectation of success that administering a cholesterol-lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol could actually prevent or delay catheter-based revascularization in patients suffering from coronary artery disease. Neither Bocan nor Jeevanandam disclose any data on prevention or delay of catheter-based revascularization in patients. Bocan only has data concerning lipid reduction in animals. Although one of skill in the art might consider it obvious to try such a method this does not equate with obviousness. One of skill in the art would not have reasonably expected such a method to work without reference to data such as is provided by the disclosure of Applicant's application. As stated above, it is in Applicant's disclosure that the support for prevention or delay of catheter-based revascularization in patients suffering from coronary artery disease is found. Applicant is the first to show that high doses of a cholesterol-lowering drug reduce the incident of an adverse cardiac event from 21% to 13%, thereby decreasing the need for revascularization. (p 25, lines 5-24). To establish a *prima facie* case of obviousness, the reasonable expectation of success must be found in the prior art references not in the Applicant's disclosure.

Because Bocan and Jeevanandam fail to teach or suggest all of the claimed elements, fail to provide motivation to combine the references and fail to provide a reasonable expectation of success, withdrawal of the rejection of claims 1-6, under 35 USC §103(a), is respectfully requested.

The Examiner has rejected claims 1, 7, and 8 under 35 USC §103(a) as being unpatentable over Bisgaier et al. US Pat No. 5,648,387 in view of Jeevanandam. The Examiner notes that Bisgaier "lacks the express disclosure of preventing or delaying catheter based revascularization." This rejection is respectfully traversed.

Bisgaier teaches the utility of dialkyl ethers in lowering Lp(a) and triglycerides, LDL, and in raising HDL-C. Bisgaier does mention in passing in col. 2, lines 49-51, that these compounds may be used to treat restenosis. Bisgaier is silent as to the use of these compounds to prevent or delay catheter-based revascularization.

As discussed above, Jeevanandam discloses two methods of revascularization for patients unable to undergo bypass surgery and does not teach or suggest anything in relation to how or if one could avoid the need for revascularization.

The prior art does not teach or suggest all the claim limitations of the present invention.

The Examiner's rejection implies that the method of Bisgaier is the same as that of the instant invention except that it is not taught to prevent the need for catheter-based revascularization. This is simply not the case. Bisgaier does not teach or suggest all elements of Applicant's claimed invention. Bisgaier does not teach or suggest administration of an amount of a cholesterol-lowering agent effective to cause an aggressive lowering of LDL cholesterol. Bisgaier is concerned with lowering Lp(a) in particular along with triglycerides and LDL while raising HDL. Bisgaier does not focus on LDL lowering and does not teach using an amount of a cholesterol-lowering agent effective to cause an aggressive lowering of LDL cholesterol.

Nor is there a teaching or suggestion of a method for preventing or delaying catheter-based revascularization. While Bisgaier does, in passing, disclose a method of treating vascular diseases such as restenosis (col 2, lines 49-51), Applicant would like to point out that treating restenosis is different than preventing or delaying catheter based revascularization where there has not been an initial surgical procedure. Restenosis refers to the reoccurrence of stenosis in a blood vessel **after** surgical correction of the primary condition (Dorland's Illustrated Medical Dictionary, 29th edition). In other words, restenosis is a treatment-related condition (iatrogenic) associated with catheter injury to the treated vessel and subsequent proliferative cellular reocclusion of the same vessel. Restenosis is **not** the same as indigenous or 'native' coronary atherosclerosis resulting from cholesterol accumulation in the vessel wall. The mechanism of restenosis is different from that of the formation of the original stenosis that necessitated surgical treatment. Restenosis involves a proliferation of smooth muscle cells in the treated artery whereas stenosis (a narrowing of a blood vessel) is thought to involve lipid deposition and the inflammatory response. Thus, Bisgaier does not disclose or suggest a method of preventing or delaying catheter-based revascularization as is claimed in the present invention. Even assuming that Jeevanandam is available as analogous prior art, Jeevanandam cannot make up for the deficiencies of Bisgaier. While Jeevanandam does describe two methods of catheter-based revascularization, Jeevanandam is silent as to revascularization with drug therapy. Thus, Jeevanandam cannot overcome the deficiencies of Bisgaier as discussed above.

There is no suggestion or motivation to modify the reference or to combine reference teachings.

Neither Bisgaier nor Jeevanandam include a suggestion or motivation to modify the Bisgaier reference to arrive at the present invention. One of skill in the art would not have been motivated by the disclosure of Jeevanandam to turn to a non-surgical method to prevent or delay the surgical method taught in Jeevanandam. Nor can motivation to modify Bisgaier be found within Bisgaier. Bisgaier does not teach or suggest that by administering the agents of Bisgaier that one would prevent or delay catheter-based revascularization as is claimed in the present application. As stated above, Bisgaier does disclose in passing, treatment of restenosis, but this is different from the present invention as it necessarily implies treatment following catheter-based revascularization. In contrast, the present invention involves treatment before surgical intervention in order to prevent or delay such surgical intervention. Bisgaier does not provide motivation for one of skill in the art to modify the method of Bisgaier to include administration of an amount of the agent to cause an aggressive lowering of LDL cholesterol. Jeevanandam does not contain any motivation to modify the method of Bisgaier to arrive at the present invention. Jeevanandam discloses two methods of revascularization for patients unable to undergo bypass surgery and does not teach or suggest anything in relation to how or if one could avoid the need for revascularization. One of skill in the art would not have been motivated by the disclosure of Jeevanandam to turn to a non-surgical method to prevent or delay the surgical method taught in Jeevanandam.

There would not have been a reasonable expectation of success.

Even assuming there was motivation to combine Bisgaier and Jeevanandam, neither the references individually or combined, provide a reasonable expectation of success that administering a cholesterol lowering agent in an amount effective to cause an aggressive lowering of LDL cholesterol could actually prevent or delay catheter-based revascularization in patients suffering from coronary artery disease. While Bisgaier does generally disclose a method of treating vascular diseases such as restenosis, as discussed above, restenosis is different from a method of preventing or delaying catheter-based revascularization. Neither Bisgaier nor Jeevanandam disclose any data on prevention or delay of catheter-based revascularization in patients. One of skill in the art would not have reasonably expected such a method to work without reference to data such as is provided by the disclosure of Applicant's application. As stated above, it is in Applicant's disclosure that the support for prevention or delay of catheter-based revascularization in patients suffering from coronary artery disease is found. Applicant is the first to show that high doses of a cholesterol-lowering drug reduce the incidence of an adverse

cardiac event from 21% to 13%, thereby decreasing the need for revascularization. (p 25, lines 5-24). To establish a *prima facie* case of obviousness, the reasonable expectation of success must be found in the prior art references not in the Applicant's disclosure.

Because Bisgaier and Jeevanandam fail to teach or suggest all of the claimed elements, fail to provide motivation to combine the references and fail to provide a reasonable expectation of success, withdrawal of the rejection of claims 1, 7 and 8 under 35 USC §103(a), is respectfully requested.

Finally, the undersigned notes that **subsequent correspondence** should be addressed to:

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Respectfully submitted,

Date: January 15, 2003

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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

10. (Amended) The method according to Claim 9 wherein the cholesterol lowering agent is selected from clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and [benafibrate] bezafibrate.